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Index of Suspicion Case Report
16 y/o boy with X-Linked Adrenoleukodystrophy
Presented as Degenerative CNS Disorders

James A. Phalen, MD, FAAP[1]
Paul G. Moe, MD, FAAP[2]

1. Developmental-Behavioral Fellow, Child Development Unit/JFK Partners
2. Child Neurologist & Professor of Pediatrics, Department of Neurology
The Children's Hospital
Denver, CO

CASE PRESENTATION (250 words maximum)

A 16-year-old boy comes to the neurologist because of new-onset seizures. He had two generalized tonic seizures one week apart. Since starting carbamazepine, he has had no further events. The boy denies recent illness or fever, and use of medications, alcohol, tobacco, or illicit substances. His mother describes problems with memory and activities of daily living.

Gestation, delivery, and early development were uneventful. He requires special education for attention-deficit/hyperactivity disorder (ADHD) and slowly worsening learning difficulties. Cognitive testing at age 13 showed a full-scale intelligence quotient (IQ) of 80.

On physical examination, the boy is of average height, but thin with a body mass index of 17.5 (5^{th} percentile). He has large ears, high-arched palate, normal-sized testes, and no pertinent skin findings. He has mild generalized hypotonia, slightly decreased sensation to vibration and proprioception in his legs, and mild ataxia on tests of coordination and gait.

A urine drug screen, serum chemistry panel, and complete blood count are normal. Lumbar puncture reveals a slightly elevated cerebrospinal fluid (CSF) protein of 51 mg/dL (normal, 15 to 45 mg/dL). Computed tomography (CT) of the brain shows hypoattenuation of the white matter and mild dilation of the posterior-lateral ventricles. Magnetic resonance imaging (MRI) with contrast shows moderately extensive symmetric deep white matter disease, mostly posteriorly, without mass effect or contrast enhancement. Electroencephalography (EEG) is normal. Neuropsychological testing reveals dementia and a 28-point drop in full-scale IQ—from 80 to 52—over the past 3 years. A blood test leads to the correct diagnosis.

DISCUSSION (900 words maximum)

Serum very-long-chain fatty acids (VLCFAs) reveal elevated C26:0 levels and high ratios of C24/C22 and C26/C22, indicating X-linked adrenoleukodystrophy (X-ALD). Genetic testing confirms the diagnosis. Tests of adrenal function are normal.

Differential Diagnosis.

This young man's new-onset seizures, dementia, and white matter abnormalities on MRI suggest a neurodegenerative disorder. Neurodegenerative disorders are a rare, diverse group of diseases. They are chronic and progressive, featuring selective and

symmetric loss of neurons in sensory, motor, or cognitive areas. They affect primarily white matter (leukoencephalopathies) or gray matter. Children may experience loss of speech, hearing, vision, strength, coordination, intelligence, or memory. Seizures and feeding problems also occur. MRI shows symmetric atrophy and/or demyelination of specific brain regions; the pattern often suggests a given disorder and prognosis. EEG abnormalities are variable. The differential includes poorly controlled seizures, congenital and chronic infection (human immunodeficiency virus), chromosomal anomalies, hypothyroidism, brain structural or mass lesions, and inhaled solvent abuse (glue sniffing).

Incidence and Cause.
Neurodegenerative disorders are inherited as autosomal recessive, X-linked recessive, or mitochondrial disorders. Although uncommon as single disorders, collectively their incidence is about 1 in 5000 births. The incidence of certain disorders is higher in some racial or ethnic groups. Single gene defects cause them. Those appearing primarily in infancy and childhood include the leukodystrophies (X-ALD, metachromatic leukodystrophy, Krabbe disease [globoid cell leukodystrophy], Zellweger syndrome, Canavan disease), mitochondrial disorders (Kearns-Sayre syndrome, MERRF [Myoclonic Epilepsy with Ragged Red Fibers], and MELAS [mitochondrial Myopathy, Encephalopathy, Lactic Acidosis, and Stroke-like episodes]), diseases of the extrapyramidal nuclei (Leigh syndrome [infantile subacute necrotizing encephalomyelopathy], early-onset Alzheimer disease in patients with Down syndrome, multiple sclerosis, Tay-Sachs disease, and Niemann-Pick disease.

Pathophysiology.
These disorders may affect multiple organ systems. By recognizing the general clinical expression and having a high index of suspicion, clinicians can narrow their differential diagnosis.

Clinical Features/Picture.
They may present at any stage of life, from the newborn period to adulthood. Their presentation is highly variable. Symptom onset depends on buildup of toxic metabolites or lack of substrate. Illness, diet, and other environmental factors affect symptoms. Thus, symptoms may wax and wane. Disorders presenting in neonates are usually severe, persistent, and progress rapidly. Those with mild neurological or behavioral symptoms may present subtly in childhood, adolescence, or adulthood.

The hallmark is a regression or unexplained plateau in development; this may evolve rapidly in days or weeks, or more insidiously over months to years. Consider a neurodegenerative disorder in any child whose mental retardation, seizures, or motor problems are unexplained. Parental consanguinity or family history of early infant death should raise suspicion. Many newborn metabolic screens do not test for neurodegenerative disorders; thus, normal results may not help. Neonates often present with symptoms similar to those of sepsis.

Evaluation.

Lessons for the Clinician. Neurodegenerative disorders may be underdiagnosed, especially those variants with delayed onset. MRI abnormalities are specific and may predate clinical findings, guiding the diagnostic evaluation. Therapy is most successful when started before symptoms appear (siblings with subclinical disease) or when minimal. A high index of suspicion is essential.

James A. Phalen, Major, MC, USAF, wrote this article while a fellow at The Child Development Unit, The Children's Hospital, Denver, CO. The views expressed in this article are those of the author and do not reflect the official policy or position of the United States Air Force, Department of Defense, or the U.S. Government.

IN BRIEF

FRAGILE X SYNDROME

Fragile X Syndrome: A Model of Gene-Brain-Behavior Relationships. Hagerman RJ and Hagerman PJ. *Mol. Gen. Metab.* 2001;74:89-97

Fragile X Syndrome: Diagnosis, Treatment, and Research. Hagerman RJ and Hagerman PJ (eds). Johns Hopkins Univ. Press, 3rd Ed. 2002.

Health Supervision for Children with Fragile X Syndrome. Committee on Genetics. *Pediatrics.* 1996;98:297-300

Fragile X syndrome (FXS) is the most common inherited cause of mental retardation. Its original name was Martin-Bell syndrome, following their 1943 study of a large pedigree of multiple males with mental retardation. They suspected an X-linked form of inheritance. In 1969, researchers found a fragile site at the distal end of the long arm of the X chromosome at position Xq27.3 in cells grown in folate-deficient media. The fragile X mental retardation 1 (*FMR1)* gene was isolated in 1991.

The mutation in the *FMR1* gene results from an expansion of trinucleotide CGG repeats. Normal individuals have 5 to 50 CGG repeats, while those with >200 repeats have the full mutation. Expansions in the 55 to 200 *premutation* repeat range are typically normal cognitively but are occasionally mildly affected. With greater CGG repeats comes increased methylation of the cytosine residues. Approximately 80% of males with the full mutation have partial or complete methylation. Hypermethylation inactivates the *FMR1* gene, thus preventing production of FMR1 protein (FMRP). FMRP regulates protein synthesis in dendritic spines. It likely has roles in neuromaturation, learning, and memory.

Males with the full mutation have FXS. Their mothers have either the premutation or the full mutation. Because sperm cells are mosaic, males with FXS pass a premutation to their daughters; however, they pass the Y chromosome to their sons, who are unaffected. Approximately 70% of females with the full mutation have cognitive deficits with an IQ < 85. Females with FXS pass the full mutation to 50% of their offspring. Males with the premutation are mildly affected or unaffected, again passing the premutation only to their daughters. Premutation

females are similarly affected, but the CGG repeats are unstable and increase in size during oogenesis/meiosis. This dynamic mutation (called the Sherman Paradox) results in anticipation; that is, younger generations are usually more affected. Mothers with >90 repeats are at nearly 100% risk of passing a full mutation to their ½ of their sons (when the mutated X is passed on).

Epidemiological data suggest a premutation carrier frequency of 1 in 100-260 females and 1 in 250-800 males in the general population. The full mutation affects about 1 in 3600 males and 1 in 6000 females. More than half of people with the full mutation go undiagnosed. Approximately 3% of individuals with previously undiagnosed mental retardation have FXS. The syndrome does not affect lifespan and occurs in all races.

Patients with FXS have a unique cognitive, behavioral, and physical phenotype. The phenotype correlates with molecular measures. Females generally have milder findings than males, correlating with the X-inactivation ratio. Early development is typical or only slightly delayed. After 12 months of age, though, delays become apparent. Up to 80% of males and 30% of females with FXS have mental retardation. Those without mental retardation typically have learning disabilities. Relative strengths are visual matching and visual perceptual skills, long-term concrete and emotional memory, verbal comprehension, and self-care. Weaknesses include higher-level thinking, abstract reasoning, complex problem solving, executive skills, expressive language, and social skills. One third of males experience a decline in IQ after puberty, due to failure to develop abstract reasoning rather than loss of intellect. Speech is perseverative with echolalia, dysrhythmia, and poor intelligibility. Up to 90% of males and 50% of females have ADHD. Sleep disturbance and feeding difficulties are common. Premutation carriers often have mood and anxiety problems. Autonomic dysregulation and hyperarousal may contribute to these problems. Over 90% of individuals exhibit autistic behaviors such as repetitive chewing, hand flapping, poor eye contact, shyness, and intolerance of changes or transitions, with up to 33% meeting criteria for autism disorder. FXS is the most common known cause of autism (2-8%). About 20% of patients experience seizures. Physical findings may be nonspecific, subtle, and unapparent until after puberty. Classic features include a long thin face, strabismus, large protuberant ears, prominent forehead and jaw, high-arched or cleft palate,

pectus excavatum, hypotonia, joint laxity, pes planus, and ataxia. Complications include scoliosis and mitral valve prolapse. Macroorchidism is universal in adult males. Up to 24% of premutation females have premature ovarian failure. Of concern are recent reports of a multisystem, progressive neurological disorder in a subgroup of premutation males over 50 years of age. Symptoms include intention tremor, ataxia, and Parkinsonian features with associated brain atrophy.

Molecular genetic testing is the gold standard for diagnosis. Southern blot and polymerase chain reaction (PCR) both determine the number of CGG repeats. Only Southern blot determines methylation status, but it gives a less accurate estimate of the number of CGG repeats if a premutation exists. Patients with undiagnosed mental retardation, global developmental delay, or autism are candidates for testing. Evaluations by occupational and physical therapists and speech/language pathologists help identify strengths and weaknesses. Therapists should then offer targeted therapy. The OT can help with sensory integration problems. An audiologist should rule out hearing loss. Educational intervention can optimize the classroom environment. A child psychologist or behavioral specialist can help decrease behavioral problems. Pharmacologic management must be individualized, targeted, and closely monitored. Stimulant medications are helpful for ADHD, while SSRIs are often used for anxiety. The pediatrician is the key to coordinating care for the patient with FXS. The American Academy of Pediatrics published health supervision guidelines for pediatricians in 1996. The guidelines fully describe FXS and provide guidance for physical examination and anticipatory guidance.

Researchers are investigating the role of nootropic drugs that target glutamate receptors. These drugs have a unique brain protecting, memory enhancing, and low toxicity side effect profile. Others are studying protein replacement therapy. Gene therapy, also under study, can rewrite the gene's protein recipe and may correct the underlying defect.

James A. Phalen, MD, FAAP

The Children's Hospital

Denver, CO

James A. Phalen, Major, MC, USAF, wrote this article while a fellow at The Child Development Unit, The Children's Hospital, Denver, CO. The views expressed in this article are those of the author and do not reflect the official policy or position of the United States Air Force, Department of Defense, or the U.S. Government.